Remarks

Claims 26-28 and 30 are pending in the application. Claim 26 has been amended. Claim 30 has been added. Support for the claim amendment and new claim can be found throughout the application, including in the Exemplification. Therefore, no new matter has been added. Moreover, the claim amendments and cancellations should not be construed to be an acquiescence to any of the claim rejections. Rather, the amendments to the claims are being made solely to expedite the prosecution of the above-identified application. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 U.S.C. § 120.

Claim Rejections Based on 35 U.S.C. § 103(a)

Claims 26-28 were rejected under 35 U.S.C. 103(a), based on the Examiner's contentions that they are unpatentable over various patents and publications. To better organize the Applicant's traverses of the Examiner's rejections under 35 U.S.C. 103(a), they are set forth below in paragraphs numbered corresponding to the numbering scheme used in the Office Action.

2. Claims 26-28 were rejected under 35 U.S.C. 103(a), based on the Examiner's contention that they are unpatentable over WO 00/47203. The Examiner states that WO 00/47203 "teaches formulations containing narcotic analgesics such as fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin for oral administration." Furthermore, the Examiner contends that "it would have been obvious to one of ordinary skill in the art to use any fentanyl based compound with hydroxypropyl-beta cyclodextrin, with a reasonable expectation of success since it is a[n] absorption enhancer." The Applicants respectfully traverse.

The Applicants respectfully contend that WO 00/47203 does not form the basis of a proper 35 U.S.C. § 103(a) rejection because one of ordinary skill in the art would have no reasonable expectation of success in enhancing the efficacy of fentanyl by adding a cyclodextrin based on WO 00/47203. As stated by the Examiner in the Office communication dated April 21, 2005, there are no examples in WO 00/47203 of using fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin. Example 6 is the only working example comprising fentanyl citrate, and this example does not specify the identity of the absorption enhancer. The applicants

respectfully argue that *regardless* of the method of administration, example 6 does not provide control data to determine if the "absorption enhancer" in question is actually enhancing absorption. The data in example 6 of WO 00/47203 only indicate that some effect on rats 636 and 637 was observed when the formulation was administered. *However, the mere observance of an analgesic effect provides no evidence of enhanced absorption because, as the Applicants have shown on page 45 of the instant application, oral administration of fentanyl alone produces a mild analgesic effect.*

It is also worth noting that administration of fentanyl citrate with the "absorption enhancer" in example 6 of WO 00/47203 produced no effect at all on rats 632, 633, and 634. *See* Tables 1 and 2 in example 6. Therefore, the Applicants contend that based on teachings and examples in WO 00/47203 one of ordinary skill in the art would have no reasonable expectation of success in enhancing the oral efficacy of fentanyl by formulating it with a cyclodextrin.

The Examiner also contends that the applicants have not shown the efficacy of the composition fitting the scope of the instant claims. In order to expedite prosecution, claim 26 has been amended and claim 30 has been added to limit the scope of the claims. In support of the amendment and new claim, the Applicants respectfully direct the Examiner's attention to page 45 of the instant application. The data in Example 1 establishes that the absorption enhancement due to the cyclodextrin increases the degree of analgesia observed relative to the control.

Furthermore, Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need for oral formulations of fentanyl. As described in the Applicants' communication dated June 18, 2004, fentanyl formulations have been known since the 1960s, and yet ACTIQ® is the only known FDA-approved oral formulation of fentanyl. However, ACTIQ®, a transmucosal formulation of fentanyl citrate, is not satisfactory because it causes nausea, vomiting, and/or a burning sensation in the mouth. Importantly, the present invention fulfills the long-felt need for a fentanyl formulation that can be administered orally. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in an assessment of nonobviousness. *See* MPEP § 2141.

Finally, the Applicants respectfully remind the Examiner that "a determination under 35 U.S.C. 103(a) should rest on all the evidence and should not be influenced by any earlier

conclusion." *See In re Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990) and MPEP § 2144.08. Specifically, the Applicants are concerned that the Examiner is reluctant to re-examine, in light of new evidence and attorney argument, conclusions reached earlier during prosecution of the instant application.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 U.S.C. 103(a) based on WO 00/47203.

3. Claims 26-28 were rejected under 35 U.S.C. 103(a), based on the Examiner's contention that they are unpatentable over WO 92/02256 in view of Farrar et al. (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989). The Examiner states that the Farrar, Portenoy, and Stanley references each teach the efficacy of fentanyl when administered orally. Furthermore, the Examiner contends that "oral administration of the compositions of fentanyl based compounds, with a reasonable expectation of success would have been obvious to one of ordinary skill in the [art] since the references of Farrar et al., Portenoy et al., [and] Stanley et al. show the efficacy of orally administered fentanyl." The Applicants respectfully traverse.

The Examiner cites page 7 line 28 through page 8, line 7 and page 11, lines 30-35 of WO 92/02256 as teaching " the properties of cyclodextrins which include solubility of hydrophobic drugs, increased bioavailability and the controlled release," and that these properties enable a proper combination with Farrar et al. Portenoy et al. or Stanley et al. The Applicants respectfully disagree. The Applicants respectfully assert that the cited passages describe the binding affinity of cyclodextrins for drug molecules, the degree of dissociation of a complexed drug with varying cyclodextrin substitutions, and the probability that these complexes could be used for administration to the neuraxis of a patient. The Applicants respectfully contend that the properties advanced by the Examiner are not described in either cited passage. Therefore, the combination would not have provided the required reasonable expectation of success vis-a-vis the rejected claims.

Moreover, the Applicants respectfully contend that WO 92/02256 in view of Farrar et al., Portenoy et al., and Stanley et al. does not form the basis of a proper 35 U.S.C. § 103(a) rejection because it is improper to combine WO 92/02256 with Farrar et al., Portenoy et al., or Stanley et al. In support of this conclusion, the Applicants respectfully remind the Examiner that "it is

improper to combine references where the references teach away from their combination." *See In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) and MPEP § 2146. Second, the Applicants respectfully contend that WO 92/02256 does not form the basis of a proper 35 U.S.C. § 103(a) rejection because there is no suggestion or motivation to modify WO 92/02256 for oral administration. The Applicants point out that the intended purpose of the invention in WO 92/02256 is to limit distribution of the drug to the neuraxis of a patient, i.e., the drug is to be prevented from dispersing throughout the body, such as by migration via the circulatory system. *See* WO 92/02256, page 1, line 27 through page 2, line 21. WO 92/02256 states "a key goal of the present invention has been to develop improved methods that will allow the routine, acute and chronic administration of agents into the neuraxis via intraventricular, epidural, intrathecal, intracisternal and related routes." *See* WO 92/02256 page 2, lines 11-14.

In stark contrast to the stated intended purpose of the invention in WO 92/02256, the instant claims are directed to oral administration of the pharmaceutical agent. Critically, after being absorbed through the intestinal wall orally administered formulations are distributed throughout the body via the circulatory system. *Hence, modifying WO 92/02256 for oral administration would render it unsatisfactory for its stated intended purpose of limiting distribution of the drug.* The Applicants respectfully remind the Examiner that "if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *See In re Gordon*, 733 F.2d 900, 221 USPQ 1125, (Fed. Cir. 1984). The Applicants contend that WO 92/02256 teaches that the distribution of the drug is to be strictly limited to the neuraxis of a patient, i.e., the drug is to be prevented from dispersing throughout the body such as by migration via the circulatory system. *See* WO 92/02256, page 1, line 27 through page 2, line 21. WO 92/02256 teaches "this vascular redistribution clearly results in powerful and acute supraspinal side effects. Such side effects are often serious and sometimes fatal." *See* WO 92/02256, page 2, line 9-10. In contrast to the teachings of WO 92/02256, the disclosures of Farrar et al., Portenoy et al., and Stanley et al. teach oral administration of fentanyl citrate which leads to *widespread distribution* of the drug throughout the body. For example, Farrar et al. teaches a lozenge comprising fentanyl citrate that dissolves in the mouth, whereby the fentanyl is absorbed through oral muscosa. *See* Farrar et al., pages 611-12. Once absorbed, the fentanyl is dispersed

throughout the entire body by the circulatory system. Hence, it is improper to combine WO 92/02256 with Farrar et al., Portenoy et al., or Stanley et al. because WO 92/02256 teaches away from methods of administration, such as oral administration, that lead to widespread distribution of the drug throughout the body.

In addition, Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need as described above in connection with the traverse of the rejection based on WO 00/47203. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in a determination of obviousness. *See* MPEP § 2141.

Finally, the Applicants respectfully remind the Examiner that "a determination under 35 U.S.C. 103(a) should rest on all the evidence and should not be influenced by any earlier conclusion." *See In re Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990) and MPEP § 2144.08. Specifically, the Applicants are concerned that the Examiner is reluctant to re-examine, in light of new evidence and attorney argument, conclusions reached earlier during prosecution of the instant application.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 U.S.C. 103(a) based on that WO 92/02256 in view of Farrar et al. (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989).

4. Claims 26-28 were rejected under 35 U.S.C. 103(a), based on the Examiner's contention that they are unpatentable over Farrar et al., or Portenoy et al., or Stanley et al. in combination with Chiesi et al., Bodor et al., Dwivedi et al., and WO 92/02256. The Examiner contends that the Farrar, Portenoy, Stanley and WO references each teach the efficacy of fentanyl when administered orally, and that what is lacking in these references is the teaching of the carrier cyclodextrin. Further, the Examiner contends that Chiesi et al., Bodor et al., and Dwivedi et al. show that inclusion complexes of cyclodextrins increase the solubility and bioavailability of drugs, and that one skilled in the art would be motivated to use cyclodextrin inclusion complexes orally since WO 92 teaches preparation of inclusion complexes of fentanyl. The Applicants respectfully traverse.

The Applicants respectfully contend that Farrar et al., or Portenoy et al., or Stanley et al. with Chiesi et al., Bodor et al., Dwivedi et al. and WO 92/02256 does not form the basis of a proper 35 U.S.C. § 103(a) rejection because it is improper to combine Chiesi et al., Bodor et al., Dwivedi et al. and WO 92/02256 with Farrar et al. or Portenoy et al. or Stanley et al. In support of this conclusion, the Applicants respectfully remind the Examiner that "it is improper to combine references where the references teach away from their combination." *See In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) and MPEP § 2146. The Applicants respectfully contend that WO 92/02256 does not form the basis of a proper 35 U.S.C. § 103(a) rejection because there is no suggestion or motivation to modify WO 92/02256 for oral administration. As discussed above, the Applicants point out that the stated intended purpose of the invention in WO 92/02256 is to limit distribution of the drug to the neuraxis of a patient, i.e., the drug is to be prevented from dispersing throughout the body, such as by migration via the circulatory system.

In stark contrast to the intended purpose of the invention in WO 92/02256, the instant claims are directed to oral administration of the pharmaceutical agent. *Hence, modifying WO 92/02256 for oral administration would render it unsatisfactory for its stated intended purpose of limiting distribution of the drug.* The Applicants respectfully remind the Examiner that "if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *See In re Gordon*, 733 F.2d 900, 221 USPQ 1125, (Fed. Cir. 1984).

As discussed above, the Applicants contend that WO 92/02256 teaches that the distribution of the drug is to be strictly limited to the neuraxis of a patient, i.e., the drug is to be prevented from dispersing throughout the body such as by migration via the circulatory system. In contrast to the teachings of WO 92/02256, the disclosures of Farrar et al., Portenoy et al., and Stanley et al. teach oral administration of fentanyl citrate which leads to widespread distribution of the drug throughout the body. Likewise, the disclosures of Chiesi et al., Bodor et al. and Dwivedi et al. teach *oral* administration of cyclodextrin complexes which leads to widespread distribution of the complexed drugs (piroxicam, carbameazepine, and an opioid peptide respectively) throughout the body, contrary to the teachings of WO 92/02256. Hence, it is improper to combine Farrar et al., or Portenoy et al., or Stanley et al. with Chiesi et al., Bodor et

al., Dwivedi et al. and WO 92/02256 because WO 92/02256 teaches away from methods of administration, such as oral administration, that lead to widespread distribution of the drug throughout the body. The Applicants respectfully remind the Examiner that "if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *See In re Gordon*, 733 F.2d 900, 221 USPQ 1125, (Fed. Cir. 1984).

In addition, Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need as described above with respect to rejection based on WO 00/47203. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in a determination of obviousness. *See* MPEP § 2141. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 U.S.C. 103(a) based on Farrar et al., or Portenoy et al., or Stanley et al. in combination with Chiesi et al., Bodor et al., Dwivedi et al. and WO 92/02256.

Double Patenting

5. Claims 26-28 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-26 of U.S. Patent No. 6,635,661 ("the '661 patent"). The Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on the '661 patent until allowable subject matter is indicated, at which point the Applicants will file a terminal disclaimer if necessary.

Fees

The Applicants believe they have provided for all required fees in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any additional required fee to our Deposit Account, **06-1448**.

Conclusion

In view of the above remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with the Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,

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